Published in final edited form as:
Pain. 2016 May ; 157(5): 1079–1084. doi:10.1097/j.pain.0000000000000484.

Opioid dose and risk of suicide

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Introduction

Suicide is a significant public health problem and preventing suicide is a national priority [41]. Emerging evidence links chronic non-cancer pain to increased risk of suicide [3; 11; 16; 18; 20; 30; 34; 37; 40]. This evidence is consistent despite significant differences in methods of pain assessment (pain level or diagnosis, use of clinical records), the population examined (clinical samples, population surveys), and the primary outcome (non-fatal attempt, suicide death). In most cases, the association between pain and suicide was partially attenuated but remains significant even after controlling for other psychiatric disorders, consistent with the interpretation that pain increases suicide risk above and beyond the association between pain and depression [5; 40].

Although these prior studies identify forms of chronic pain as markers of increased suicide risk, none have examined pain treatment as a potential additional indicator of risk among those with pain. With regard to suicide risk, the treatment of pain is a controversial topic. Some have expressed concern that the under-treatment of pain could place individuals with pain at elevated risk for suicide [20]. However, prescription opioids are being increasingly used in the United States to treat chronic pain [19] and it is possible that access to opioids, and specifically to large quantities of opioids, could increase the risk of suicide in those with chronic pain. Overall, the utility of opioids for chronic pain is disputed as there is little evidence for the efficacy of chronic opioid therapy while the potential harms of opioid use increase in a dose-response manner [6]. Increased risk of suicide with greater use of opioids is consistent with the broader suicide literature, which has consistently documented a link between suicide rates and access to potentially lethal means of suicide [36] as well as existing Department of Veterans Affairs and Department of Defense treatment guidelines that describe higher suicide risk as a relative contraindication for opioid therapy [9]. Prior work has found a dose-response relationship between opioid dose and increased risk of

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All authors report no conflicts of interest, and all authors report that they have no financial relationships with commercial interests.

unintentional poisoning (often called overdose) [2; 10]. Yet, a recent study of Veterans Health Affairs (VHA) patients indicated that most suicides involve firearms, and the proportion of suicides that involve overdose is not noticeably different in those patients with a diagnosed pain condition relative to those without a pain condition [16]. Importantly, in those patients with a diagnosed pain condition, increased opioid doses could also be a marker for greater pain severity or poorly controlled pain, as opioid doses are typically increased when lower doses and other treatment options have failed to provide adequate pain management. Thus, a link between increased opioid dose and suicide could be seen even if no causal link exists between the opioid dose and suicide risk given the association of pain severity with suicide risk [17].

The present study was designed to examine opioid dose as a potential marker for increased risk for suicide by investigating the association between opioid regimen and risk of suicide mortality among VHA patients with chronic pain who received an opioid.

Methods

Study Population

This study used a case-cohort design [31], drawing from the base population of all VHA patients for fiscal years (FYs) 2004–2005 nationally. For each of the two study years, a 5% random sample of patients was drawn, irrespective of case status. Cases were all FY04-FY05 VHA patients who died by suicide before the end of FY09. Both cases and controls were further restricted to all individuals with a chronic pain condition who were treated with opioids (see below for clarification of these categories). Individuals with indicators of palliative care consultations or hospice care in their VHA medical records were excluded (n=1926). The sample size was 123,946. This project received approval from the Ann Arbor VA Human Subjects Committee.

Data Sources

As part of ongoing VA suicide monitoring and evaluation activities, data from the VA National Patient Care Database (NPCD) were linked to outpatient prescription medication data from the VHA's Pharmacy Benefits Management Services and VA search results from the Centers for Disease Control and Prevention's National Death Index (NDI). The NPCD data were used to identify all individuals who utilized any services in FY04 or FY05 and they include information on treatment utilization, demographic characteristics and clinical diagnoses for all treatment contacts of patients seen anywhere in the VHA. The NDI contains information on date and cause of death.

Suicide mortality

The process for ascertaining death from suicide is described more comprehensively elsewhere [see [14; 25]]. Briefly, for all individuals who utilized VHA services in FY04-FY05, VHA services use was examined in FY10. NDI searches were conducted for all individuals who received VHA services in FY04-FY05, were alive at the start of FY04, and did not have VHA service use in FY10 (which would indicate survival through the end of

the study period). In instances where the NDI search yielded multiple potential matches, Sohn and colleagues' [39] procedures were utilized to identify the best match.

Measures

Primary outcomes—*Suicide mortality* was based on deaths classified by the International Classification of Diseases-10 (ICD-10) codes X60-X84 and Y87.0 [44] in the NDI; *intentional overdose* was identified by ICD-10 codes X60-X69.

Predictors—This study focused on *maximum prescribed morphine-equivalent daily opioid dose* and *opioid fill type* as the primary predictors of interest. Morphine-equivalent doses were calculated for codeine, morphine, oxycodone, hydrocodone, oxymorphone, and hydromorphone using established methods [2; 12; 32]. The present analyses did not examine synthetic opioids (which include buprenorphine) or methadone. This was done in order to focus on agents used to treat chronic pain, instead of the treatment of opioid dependence. In addition, there is little consensus on the best methods to use to calculate morphine equivalent dose for methadone. This creates the potential to over- or under-estimate the relationship between overall opioid dosage and suicide because methadone usage is known to be associated with overdose risk. The specific formula for calculating morphine equivalent dose is provided as a footnote at the bottom of Table 2. An as-prescribed approach was used to measure maximum daily dose [42]. The daily doses of all prescription fills that covered that particular day were summed to calculate a total maximum daily dose for each day of the study observation period. The specific daily dose for each fill was determined by dividing the total morphine-equivalent milligrams dispensed in that fill by the number of days supplied. Maximum morphine equivalent daily opioid dose was modeled as time-varying and recoded into categories: 0 mg, 1 to <20 mg/d, 20 to <50mg/d, 50 to < 100mg/d, and 100+mg/d [2; 10]. These dosage categories were chosen to allow for comparison to other published work on unintentional overdose [2] as well recent recommendations that caution against prescribing more than 90–100mg/d [26]. In order to avoid double-counting dosage, opioid fills that appeared to be continuations of the same treatment plan (i.e., were the same opioid formulation and dosage) were assumed to not start until the end of the days' supply of the prior fill. Also consistent with the Bohnert paper [26], for each day that an individual had at least one opioid prescription, a 3-level time varying indicator of *opioid fill type* was calculated to reflect schedule, with the categories of: only regularly scheduled opioids; only PRN opioids; or both a regularly scheduled opioid and PRN opioid prescriptions.

Other covariates—Pain and other physical conditions were:, headache (339.x,346.x, 307.81,784.0,350.2), neuropathy (337.0,337.1,355.x,356.x,357.x, 377.x), chronic pain (338.0,338.2,338.4,354.4, 355.71,354.0, 355.5,710.x-729.x, 731.x-738.x), acute pain (800.x-959.x,338.1), chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), and sleep apnea (250.x,272.0,272.1,272.2,272.3,272.4,278.00,278.01,401.x-405.x, 410.x-414.x,430.x-438.x,491.x,492.x,494.x,496.x,780.51,780.53,780.57,783.1), and cancer (140.x-239.x,338.3). Psychiatric conditions were: depression, bipolar disorder, mood NOS (293.83,296.2,296.3,296.90,296.99, 298.0,300.4,301.12, 309.0,309.1,311, 296.0–296.1, 296.4–296.8), psychotic disorders (295.0–295.4,295.6–295.9,297.0–297.3,297.8–298.4,298.8,298.9), substance use disorders (291,292,303.0,303.9,304.0–304.9,305.0,305.2–

305.9), Post-Traumatic Stress Disorder (309.81), and other anxiety disorders (300.00,300.01,300.02,300.09,300.10,300.20–300.23,300.29). The Charlson Comorbidity Index [4; 33] was used to measure medical comorbidity based on ICD-9-CM codes and recoded as 0, 1, or ≥2 conditions. Age in years at the start of FY04 was divided into the following categories to match existing research on suicide risk in Veterans [25]: 18–29, 30–39, 40–49, 50–59, 60–69, and 70 years or older. Race (coded as White, Black, and Other/missing) and Hispanic ethnicity were also included in the analyses.

Analyses

The suicide rates associated with specific opioid prescribing characteristics (dose and schedule) were estimated by accounting for the case-cohort design. To do so, we first calculated the cumulative number of suicide deaths that occurred under each of the opioid prescribing conditions (e.g., number of patients who died while prescribed a particular dose). The denominator for each rate was calculated in two steps. First, we summed the person-years contributed by the random sample under each opioid prescribing characteristic. These values were then multiplied by the inverse of sampling fraction (the proportion of all VHA patients for FY04 or FY05 who were selected under the random sampling scheme) in order to provide an estimate of the person-time for each opioid treatment characteristic that would have been observed for the entire population, had pharmacy data for the entire population been available. This method was necessary because the cases were drawn from the entire population and not just the random sample. Consequently, all rates are estimated rather than directly observed. Cox proportional hazards models were used to examine the relationship between opioid regimen and suicide death adjusting for demographic and clinical characteristics. All multivariable models were restricted to periods of time when individuals were prescribed at least one opioid. A risk-sets approach and a robust variance estimator were used for the multivariable modeling [22].

Results

A total of 2,601 patients died by suicide during the observation period; 1,669 (64.2%) of suicides were due to firearms, 532 (20.5%) to an overdose, and 252 to strangulation (9.7%). Table 1 describes differences between those who died by suicide and those who did not.

The rates of suicide per 100,000 person years by any mechanism were 44.4 (95% confidence interval (CI) 42.3, 46.5) when the maximum prescribed dose was 0 mg and 105.0 (95% CI 88.4, 123.1) when the maximum dose prescribed was 100+mg/d (see Table 2). Estimated unadjusted rates of suicide per 100,000 person-years were 67.9 (95% CI 60.4, 76.0) during time periods with only regularly scheduled doses, 54.9 (95% CI 50.1, 59.9) with only PRN doses, and 90.1 (95% CI 73.7, 108.2) during periods with both regularly scheduled and PRN doses. Rates of suicide by intentional overdose ranged from 8.2 (95% CI 7.3, 9.1) per 100,000 person years when the maximum prescribed dose was 0 mg to 27.8 (95% CI 19.5, 37.4) per 100,000 person years when maximum prescribed dose was 100 milligrams or more. By fill type, the rates per 100,000 person years were 17.5 (95% CI 13.8, 21.7) for time periods with only regularly scheduled doses, 12.8 (95% CI 10.6, 15.3) with only PRN doses, and 24.0 (95% CI 16.0, 33.7) during periods with both regular and PRN doses.

In models examining the association of opioid regimen with risk of suicide, a relationship was observed with opioid dose. A prescribed dose of 1 to <20 mg/d was the reference group and the estimated adjusted hazard ratios were: 1.48 (95% CI 1.25, 1.75) for 20 to <50mg/d, 1.69 (95% CI 1.33, 2.14) for 50 to <100mg/d, and 2.15 (95% CI 1.64, 2.81) for 100+mg/d. Opioid schedule was not significantly associated with suicide risk in the adjusted models. Similarly, for models specifically examining intentional overdose, with 1 to <20mg/d as the reference group, the adjusted hazard ratios were: 1.59 (95% CI 1.12, 2.27) for 20 to <50mg/d, 1.74 (95% CI 1.09, 2.76) for 50 to <100mg/d, and 2.09 (95% CI 1.22, 3.56) for 100+mg/d. Opioid fill type was not significantly associated with intentional overdose in the adjusted models.

Supplementary Analyses

An additional analysis examined the relationship between total opioid dose and suicide when tramadol was included in the calculation of total opioid dose. The results of this analysis indicate that the association between opioid dose and suicide was still present when including tramadol, although to a somewhat lesser magnitude than in the primary analyses. Specifically, adjusted hazard ratios were 1.45 (95% CI 1.21, 1.72) for 20 to <50mg/d, 1.47 (95% CI 1.17, 1.84) for 50 to <100mg/d, and 1.69 (95% CI 1.36, 2.10) for 100+mg/d.

To examine the potential connection between suicide and other medications used to treat pain, we conducted additional analyses testing for associations between acetaminophen dose and regimen and suicide risk. Estimated unadjusted rates of suicide per 100,000 person-years were 45.4 (95% CI 40.4, 50.8) when the maximum prescribed dose was 0 mg and 63.0 (95% CI 36.7, 96.3) when the maximum dose prescribed was 3000+mg/d. Suicide rates were 53.8 (95% CI 40.5, 68.9) during time periods with only regularly scheduled doses, and 54.8 (95% CI 33.9, 80.5) with only PRN doses.

Discussion

This study examined the association between prescribed opioid dose and suicide in a national sample of VHA patients with a chronic non-cancer pain condition who received opioid therapy. Increased dose of opioids was found to be a marker of increased suicide risk, even when relevant demographic and clinical factors were statistically controlled. The type of opioid dosing schedule did not significantly affect suicide risk after accounting for other factors. Similar to the general US population and other large studies of VHA patients [16; 35], the vast majority of suicides involved firearms, with overdose accounting for approximately 15–20% of all suicides. The strength of association between opioid dose and suicide was essentially the same when looking specifically at overdose-related suicides compared to all suicides. In addition, in supplementary analyses, there was no significant association between acetaminophen dose and regimen and suicide risk, suggesting that the observed effects may be specific to opioids. Overall, these findings highlight a potential link between opioid dose and suicide in those with pain but also suggest that this relationship is likely more complicated than an increase in access to opioids leading to an increase in intentional overdoses.

The use of prescription opioids as a frontline treatment for chronic pain has increased sharply in the past decade [19]. This has corresponded with a number of adverse outcomes, including increases in the prevalence of opioid misuse and unintentional overdose [28; 29; 43]. Prior work has described a dose-response association between daily opioid dose and risk of unintentional overdose [2; 10; 13]. The present study documents a similar relationship between daily opioid dose and suicide risk. However, the magnitude of the association with suicide is somewhat lower than what has been described for unintentional opioid overdose in a similar sample of VHA patients [2]. Given the observational design of the present study, it is not known whether suicide should be conceptualized as an adverse outcome of opioid use or if opioid dose is merely a marker of increased pain duration and/or severity, or suboptimal pain management efforts.

Prior work focused on suicide risk in those with chronic pain has highlighted the potential importance of examining the impact of pain treatment [40]. However, to the best of our knowledge, this has not been done previously. Although many possible explanations exist for why opioids may relate to suicide risk, two potential reasons for this relationship are that either: (1) under-treatment of pain in those with chronic pain conditions could increase the risk of suicide [20] or (2) providing opioids to those with pain could increase the access to a potentially lethal means of suicide in a group known to have high rates of co-occurring psychiatric disorders. The finding that suicide risk increased along with opioid dose might seem to counter the hypothesis that under-treatment of pain increases suicide risk. However, it is important to note that, in many cases, increased opioid use may not result in significant long-term reductions in pain or improvements in functioning [23]. Moreover, greater clinical reliance on opioid therapy may be a marker for poor access to other effective pain management options (e.g., cognitive behavioral therapies, physical therapy, multidisciplinary pain treatment). Clinicians and patients faced with unmanaged pain and no access to non-pharmacological treatment options may choose to increase opioid dose due to lack of other options. In addition, prolonged exposure to opioids can induce hyperalgesia, or an over-response to painful stimuli [7] and others have hypothesized that increased sensitivity to pain may explain the association between opioid use and prior suicidal behaviors [27]. However, directly testing the impact of poorer access to treatment and/or greater sensitivity is not possible with the current data.

This study cannot answer the question of whether increased access to opioids increases suicide risk by providing individuals with access to a potentially lethal means of suicide. Yet, the fact that a stronger relationship was not found for suicide by overdose suggests that the relationship between opioids and suicide may be more complicated than just the increased use of opioids as a method for suicide. This is consistent with other work, which has found that the vast majority of suicides among those with substance use disorders do not involve overdose [15]. One alternative explanation for a direct association between opioid use and suicide is that the disinhibiting effects of higher doses of prescription opioids could increase the likelihood that individuals with suicidal thoughts or plans could act on these impulses [8]. It is also possible that the observed association between higher opioid dose and suicide may not be due to the direct impact of opioids but may, instead, be due to the characteristics of the individuals who receive elevated opioid doses. This confounding or selection effect could reflect the impact of the presence of specific psychiatric or pain

conditions, poorer sleep or functioning in those who receive higher opioid doses compared to lower doses. Other psychological or contextual factors such as hopelessness, increased stigma or frustration with the quality of one's care cannot be measured within the present data and may explain why those who receive more opioids are more likely to die by suicide. In the present study, associations between opioid dose and suicide remained significant in the presence of specific psychiatric conditions, which argues against psychopathology as an alternative explanation for the effect of opioid dose on suicide. However, it is likely that many psychiatric and substance use disorders were not detected during usual care and residual confounding could still partially or fully account for the observed associations between opioids and suicide.

Another possibility is that the prescription of high doses of opioids is a marker of help-seeking for pain that exceeds the patient's ability to cope. The difficulties of attributing effects in suicide to specific medications in observational research are not unique to opioids and others have concluded that no observational study can fully account for potential confounders [21]. Even if the observed increase in suicide risk is not directly caused by opioid dose, the present findings highlight the importance of greater monitoring and treatment for suicide risk among those receiving higher opioid doses. Also, to the extent that higher opioid doses reflect longer duration of pain, greater pain severity, and/or ineffective pain treatment, results point to the importance of optimizing pain management strategies among those with severe and/or uncontrolled pain.

This study has additional limitations worth noting. Individuals in this study are VHA patients and the findings may not generalize outside the VHA. Suicide rates in the VHA are higher than age- and gender-matched individuals in the US population and risk factors [1; 24], such as pain and opioid dose, may also function differently in the VHA. Also, the fact that all individuals in this study were receiving care from a large integrated healthcare system could influence the ways in which aspects of care relate to suicide risk. The analyses also did not account for other CNS depressants, duration of prior opioid prescription, or recent changes in opioid dose. In addition, the as-prescribed approach utilized to model the association between opioid dose and suicide only examines the dose of the medication provided, not the amount consumed. It is likely that some individuals deviated from their prescription [38] and this is not captured in these analyses. In addition, sample sizes for some subgroups (e.g., opioid dose of 100mg+) were relatively low, resulting in wider confidence intervals for point estimates of suicide rates. The present models did not include duration or severity of chronic pain, and it is possible that longer pain duration and/or greater pain severity may predict both higher opioid dose and increased suicide risk.

Even with these limitations, this study is the first to examine the link between opioid dose and suicide mortality in those with chronic pain. The present findings indicate that greater opioid dose is a marker for increased suicide risk. In addition, the present results indicate that this relationship is not limited to suicide by overdose but that opioid dose is associated with a broader array of suicide methods. A high priority for future research is the assessment of the common and unique effects of opioid use and pain chronicity and/or severity on suicide risk. Testing for longitudinal associations between opioid use, pain duration and severity, and surrogate endpoints (e.g., suicidal ideation) might better illuminate the

mechanisms whereby opioid use may lead to greater suicide risk. In addition, identification of subgroups that may be more or less susceptible to opioid-related adverse outcomes will inform clinical efforts to develop optimal pain management strategies that do not carry added risk for suicide. Finally, although the present design cannot determine the causes of the link between opioids and suicide, clinicians treating patients with pain who are receiving higher doses of opioids should be aware of the increased suicide risk and monitor suicidal thoughts and plans in these patients. It is possible that a greater attention to suicide risk, combined with increased psychiatric treatment and utilization of other pain management strategies, might help to mitigate the increased risk for suicide among pain patients receiving higher doses of opioids.

Acknowledgments

Study data and analyses represent VHA suicide monitoring and evaluation activities. Input from senior mental health leadership at VHA Central Office helped shape the design and conduct of the study, the collection, management, analysis, and interpretation of the data, and the preparation, review, and approval of the manuscript. The views expressed in this report are those of the authors, and do not necessarily represent those of the VHA. Dr. Ilgen takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors report no conflicts of interest. We appreciate the earlier feedback that we received on earlier drafts of this manuscript from Jodie Trafton, Ph.D. and Robert Kerns, Ph.D.

Funding support: This work was supported by the Veterans Health Administration (VHA). Data were acquired for program planning and evaluation purposes. This specific study was also partially supported by the VHA's Health Services Research and Development Service (HSR&D) Career Development Award (CDA-09- 204; A.S.B.B.). The views expressed in this report are those of the authors, and do not necessarily represent those of the VHA. Authors had full access to all of the data in the study, and Dr. Ilgen takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1

Patient characteristics (N=123,946).

	Suicide Deaths (N=2601) N (%)	Random Sample (N=121,345) (N%)	p-value
Demographics			
Male	2499 (96.1)	112,453 (92.7)	<.0001
Female	102 (3.9)	8892 (7.3)	
Age			<.0001
18–29	59 (2.3)	3015 (2.5)	
30–39	160 (6.2)	6841 (5.6)	
40–49	556 (21.4)	19,311 (15.9)	
50–59	819 (31.5)	40,209 (33.1)	
60–69	412 (15.8)	22,687 (18.7)	
70+	595 (22.9)	29,282 (24.1)	
Race			
White	2171 (83.5)	88,698 (73.1)	<.0001
Black	121 (4.7)	20,322 (16.8)	
Other/Missing	309 (11.9)	12,325 (10.2)	
Hispanic Ethnicity	64 (2.5)	5689 (4.7)	<.0001
Physical Conditions and Pain			
COPD/CVD/Sleep Apnea Dx	1954 (75.1)	99,251 (81.8)	<.0001
Chronic Pain Dx	2472 (95.0)	116,006 (95.6)	0.169
Headache Dx	286 (11.0)	11,047 (9.1)	0.001
Injury/Acute Pain Dx	572 (22.0)	24,991 (20.6)	0.082
Neuropathy Dx	274 (10.5)	13,704 (11.3)	0.226
Cancer Dx	530 (20.4)	27,220 (22.4)	.0129
Psychiatric Conditions			
Depression, Bipolar, mood NOS Dx	1154 (44.4)	32,698 (27.0)	<.0001
Other Anxiety Dx	423 (16.3)	11,082 (9.1)	<.0001
PTSD	383 (14.7)	15,338 (12.6)	0.002
Psychotic Disorders Dx	163 (6.3)	4425 (3.7)	<.0001
Substance Use/Dependence Dx	513 (19.7)	12,252 (10.1)	<.0001
Charlson Comorbidity Index Score			
0	1160 (44.6)	49,883 (41.1)	.001
1	631 (24.3)	29,839 (24.6)	
2+	810 (31.1)	41,623 (34.3)	

Table 2

Unadjusted rates of suicide deaths by opioid dose and fill type.

	Deaths (n)	Person-Years	Rate/100,000 PY (95% CI)
Suicide, Any Mechanism			
Prescribed Daily Opioid Dose			
0	1716	3,862,873	44.4 (42.3, 46.5)
1 to < 20 mg/d *	218	508,852	42.8 (37.3, 48.7)
20 to < 50 mg/d *	395	618,533	63.9 (57.7, 70.3)
50 to < 100 mg/d *	132	174,839	75.5 (63.2, 88.9)
100+ mg/d	140	133,284	105.0 (88.4, 123.1)
Fill Types			
Regularly Scheduled Only	291	428,362	67.9 (60.4, 76.0)
PRN Only	489	890,666	54.9 (50.1, 59.9)
Simultaneous PRN and Regularly Scheduled	105	116,480	90.1 (73.7, 108.2)
Intentional Overdose, Any Substance			
Prescribed Daily Opioid Dose			
0	315	3,862,873	8.2 (7.3, 9.1)
1 to < 20 mg/d *	47	508,852	9.2 (6.8, 12.1)
20 to < 50 mg/d *	99	618,533	16.0 (13.0, 19.3)
50 to < 100 mg/d *	34	174,839	19.4 (13.5, 26.5)
100+ mg/d	37	133,284	27.8 (19.5, 37.4)
Fill Types			
Regularly Scheduled Only	75	428,362	17.5 (13.8, 21.7)
PRN Only	114	890,666	12.8 (10.6, 15.3)
Both Regularly Scheduled and PRN	28	116,480	24.0 (16.0, 33.7)

* The following formula was used to calculate morphine equivalent doses: dose = (size_mg)*(tl_qty/day_supply); Conversion factors multiplied by dose to get morphine equivalencies: CODEINE =.15; HYDROCODONE=1; HYDROMORPHONE=4; OXYCODONE=1.5;OXYMORPHONE=.56; HYDROMORPHONE (injected)=16;MORPHINE (injected)=3

Table 3

Cox proportional hazards models of risk of death by suicide.

	Suicide, Any Mechanism	Intentional Overdose
Treatment and Patient Characteristics	**HR (95% CI)**	**HR (95% CI)**
Prescribed Daily Opioid Dose		
1 to < 20 mg/d	1.00	1.00
20 to < 50 mg/d	1.48 (1.25, 1.75)	1.59 (1.12, 2.27)
50 to < 100 mg/d	1.69 (1.33, 2.14)	1.74 (1.09, 2.76)
100+ mg/d	2.15 (1.64, 2.81)	2.09 (1.22, 3.56)
Opioid Fill Type		
Regularly Scheduled Only	1.00	1.00
PRN only	1.08 (0.92, 1.27)	1.12 (0.83, 1.52)
Simultaneous PRN and Regularly Scheduled	1.07 (0.82, 1.41)	1.10 (0.64, 1.87)
Physical Conditions and Pain		
COPD/CVD/Sleep Apnea Dx	0.76 (0.63, 0.90)	0.58 (0.43, 0.79)
Chronic Pain Dx	0.76 (0.53, 1.09)	0.83 (0.41, 1.69)
Headache Dx	1.07 (0.86, 1.35)	1.08 (0.73, 1.60)
Injury/Acute Pain Dx	0.98 (0.82, 1.17)	1.05 (0.76, 1.46)
Neuropathy Dx	0.89 (0.71, 1.12)	1.20 (0.77, 1.86)
Cancer Dx	1.16 (0.98, 1.38)	0.94 (0.64, 1.40)
Psychiatric Conditions		
Depression, Bipolar, mood NOS Dx	1.44 (1.24, 1.68)	2.40 (1.78, 3.23)
Other Anxiety Dx	1.34 (1.11, 1.61)	1.29 (0.92, 1.81)
PTSD	0.81 (0.66, 0.99)	0.78 (0.54, 1.13)
Psychotic Disorders Dx	1.56 (1.15, 2.12)	2.41 (1.50, 3.87)
Substance Use/Dependence Dx	2.04 (1.69, 2.46)	2.00 (1.44, 2.78)
Charlson Comorbidity Index Score		
0	1.00	1.00
1	1.14 (0.96, 1.36)	1.18 (0.85, 1.64)
2+	1.05 (0.88, 1.26)	0.88 (0.60, 1.28)
Cancer Diagnosis	1.16 (0.98, 1.38)	0.94 (0.64, 1.40)

	Suicide, Any Mechanism	Intentional Overdose
Treatment and Patient Characteristics	**HR (95% CI)**	**HR (95% CI)**
Demographics		
Male	2.07 (1.43, 2.99)	0.94 (0.59, 1.50)
Age (Reference: 18–29)		
30–39	0.86 (0.47, 1.60)	1.26 (0.43, 3.72)
40–49	0.91 (0.52, 1.60)	1.44 (0.52, 3.99)
50–59	0.70 (0.40, 1.23)	0.84 (0.30, 2.35)
60–69	0.81 (0.45, 1.44)	0.58 (0.19, 1.74)
70+	1.07 (0.60, 1.91)	0.56 (0.18, 1.75)
Race (Reference: White)		
Black	0.27 (0.19, 0.38)	0.28 (0.14, 0.55)
Other/Missing	0.56 (0.44, 0.73)	0.71 (0.42, 1.20)
Hispanic Ethnicity (Reference: Non-Hispanic)	0.66 (0.41, 1.06)	1.18 (0.59, 2.36)
Ethnicity Unknown	3.52 (2.94, 4.21)	3.29 (2.23, 4.84)